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THE UNDESIRED AND UNEXPECTED ACTIONS OF MEDICINES.

(INCLUDING TOLERANCE AND IDIOSYNCRASY TO, OR ABNORMAL RESULTS FROM, ORDINARY DOSES.)

Being a Paper read in the Section of Pharmacology at the Annual Meeting of the British Medical Association at Manchester, July–August, 1902.*

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THE subject which I have to introduce is a very large one, and the time at my disposal is short. I cannot, therefore, do more than give a brief outline. In preparing this sketch, I must acknowledge my obligations to two books which gave me a great deal of information on the subject, namely, Lewin's *Nebenwirkungen der Arzneimittel* and Battistini's *Rimedi Nuovi.*

Drugs may exert an unexpected action either by (1) failing to produce their usual effect; (2) having an excessive effect, or (3) having an unusual effect. In discussing the action of drugs, we must always remember it is really the reaction between the drug and the organism which we are considering, and an alteration in the effect may be either due to the drug or to the organism. It is necessary to insist upon the fact that we are apt in prescribing to be misled by names and to think that what we have administered to our patients under a certain name is always the same thing. One of the saddest cases of this is that of Mr. Myer, of Winschoten in Holland,† who prescribed aconitine for a patient in what he thought to be a perfectly safe dose, and, as the patient complained of the effects, he took a double dose of it himself, with the result that he died in the course of five hours. Nor was this fatal result much to be wondered at, because pure aconitine is three hundred or four hundred times as strong as the old German preparation. Such extreme cases are fortunately rare, but I believe it is by no means unfrequent that cascara sagrada

* Reprinted from the *British Medical Journal*, October 11th, 1902.

† Kunkel, *Toxikologie*, p. 768.

fails to produce its effeet beeause the bark has been seeured from the wrong species of rhamnus. But even when proeured from the same plant, tinctures and other preparations may differ very much in strength, according to the plaee where the plant is grown, and its age, espeeially as to whether it is flowering or not. Moreover, many plants contain more than one active principle, and sometimes these aetive principles are antagonistic to one another.

Another source of error is, that plants may have deteriorated by keeping in the druggist's shop and so lost their original virtues. Or in the hands of the purehaser they may have changed their strength or aetion.

I remember reading the case of a child who was said to have died from one drop of laudanum, but this laudanum had been kept on a mantelshelf for a considerable time and the mouth of the bottle only stopped by a twisted piece of paper, so that the original tincture of opium had become converted into a strong liquid extract by evaporation. Badly-preserved solutions of morphine appear sometimes to undergo ehange, with the formation of apomorphine or some other produet which gives rise to vomiting. Occasionally, the very purity of drugs may alter their effect for the worse. It was first pointed out by Professor Leech, whose early death every one who knew him deeply deplores, that artificial sodium salicylate owes its inferiority to natural salicylate not to the presenee of any impurity, but really to the absence of a certain amount of methyl salicylate whieh exists in the natural product.

Some time ago, when preseribing potassium nitrate, with the view of lessening high arterial tension and arresting epistaxis, I found that the patient was immediately relieved by the use of saltpetre, which he got from an oilshop. On having the prescription made up at a chemist's with pure potassium nitrate the epistaxis began again. When he told me this, I suspected that the ordinary saltpetre contained a small amount of nitrite, and on adding about half a grain or a grain of sodium nitrite to the 15 or 20 grains of potassium nitrate that he had been taking, the epistaxis again ceased immediately. This result explained to me the observation made by a very

old doctor, who told me that although he belonged to a very gouty family, he kept away gout by taking 20 grains of nitrate along with 15 or 20 grains of potassium bicarbonate in a large tumbler of water every morning, and the nitre that he got from a gunmaker was always better than what he got from a chemist. This was probably due to a small admixture of nitrite which tended to keep down the high tension which his gouty kidneys would otherwise have produced.

In the case of most drugs, we are obliged simply to trust to the knowledge and professional position of the chemist who supplies us, but occasionally even this may fail, and it is well to be on the outlook for the possible presence of impurities. On one occasion, when seeing a patient in consultation with another doctor, I noticed a strong smell of onions and concluded that the patient had been having bismuth contaminated by tellurium, which rare metal gives rise to the unpleasant so-called "bismuth breath." I soon found, however, that it was the doctor who had been taking the bismuth, and on inquiry we found that it had been obtained from one of the best firms of chemists in the three kingdoms, and the quantity of impurity was so small as to be imperceptible to chemical tests, and its presence was only detected by the still more delicate physiological test. Alterations in the effect of drugs may depend very much upon changes in them after they had been actually swallowed. In tropical countries quinine is often swallowed by the teaspoonful, and a great part of this is often wasted because there is an insufficient amount of acid in the intestinal canal to dissolve it. Should, however, a patient take quinine in this way, and have several lemon squashes immediately afterwards, the citric acid in them might cause so much quinine to be dissolved and absorbed as to give rise to buzzing in the head, both unpleasant and unexpected. In persons who live upon a vegetable diet and are accustomed to take but little salt, calomel appears only to have a slight action, but in people who take a lot of salt, or are accustomed to live upon salt provisions, a larger quantity of the calomel taken is converted into corrosive sublimate, and thus the medicine may have an unexpectedly

violent action. An unusual amount of hydrochloric acid in the stomach may perhaps produce a like result, and this is a point to be borne in mind, because nitrohydrochloric acid and calomel are both favourite remedies in conditions of biliousness. Sulphide of antimony, on the other hand, is dissolved by alkalies, and an excessive amount of alkali given along with this remedy may tend to produce gastro-intestinal irritation. This is to be borne in mind when giving compound calomel pill along with alkalies, because this pill contains sulphide of antimony. Resinous drugs are insoluble in acids, but freely soluble in alkalies. This is to be borne in mind when giving resinous purgatives, such as aloes, scammony, jalap, and podophyllin, and advantage has been taken of the power of alkalies to keep the resin in solution in the old-fashioned and very useful but very disagreeable, compound decoction of aloes.

The relationship of medicines to meals is very important, and, perhaps, of this no better example can be given than arsenic which, if taken in full doses before a meal, will almost certainly cause gastro-intestinal irritation, whereas the same dose will produce no disagreeable symptoms if taken immediately after a meal, so that the medicine becomes diluted by admixture with the food in the stomach.

Perhaps I can not do better in introducing this subject than take a typical drug like arsenic and consider its different actions and afterwards compare them with those produced by other drugs. A drug may act on the body (1) at the point of application, whether it be skin, subcutaneous tissue, raw wound or mucous membrane. After its absorption it may act (2) upon any organ of the body to which it is carried by the blood. It may act (3) during its elimination upon the same parts on which it usually acts during its absorption, namely, the skin and mucous membranes, as well as another great eliminating organ, namely, the kidneys. The action of any drug whilst circulating in the body depends to a great extent on the amount present in the blood, and this amount is determined by the difference between the quantity absorbed and the quantity excreted in a given time. If absorption be rapid and excretion slow, much of the drug will circulate, whereas if absorption be

slow and excretion rapid, very little will be present in the blood at any one time. A drug may act at one time more violently (*a*) upon the point of application, (*b*) at another on the organs to which it is carried by the blood, and (*c*) at yet another on the organs of elimination. A large dose of arsenic taken by the stomach will irritate that organ and may be ejected by vomiting without being absorbed to any extent, thus leaving untouched the organs generally as well as the channels of elimination.

John Hunter and Sir Benjamin Brodie showed that when arsenic was applied to a wound it was absorbed with rapidity and was eliminated very rapidly by the mucous membrane of the stomach, so much so that it produced inflammation of the stomach before any appearance of inflammation showed itself in the wound. But arsenic has long been used as a secret remedy in cases of cancer, and often it causes the part to slough away without having any general action, although every now and again cases of poisoning have occurred. The chief rule for avoiding any poisonous action in such cases is said to be to use the arsenical paste very strong and over a small area. If used in too dilute a form the arsenic is absorbed, but if used very strong it forms a local slough and is not absorbed at all.

In the poisoning by beer in Manchester the arsenic was so much diluted that it appeared to have little local action when drunk, but after absorption it was carried to the mucous membrane of the stomach and intestines, and during its elimination by these organs gave rise to sickness and diarrhœa. During its elimination also by the skin it produced many cutaneous eruptions, and while circulating in the blood gave rise to neuritis, anæmia, fatty degeneration of the liver, muscles and heart, with muscular weakness, loss of sensibility, great pain, and a tendency to syncope. In the cases of poisoning by arsenic in beer, the drug was taken in small quantity at a time and in a state of dilution that prevented its local action on the intestinal canal, but its ingestion was so continuous that the eliminating organs could not get rid of it as quickly as it was absorbed, and so it accumulated in the

organism. Exactly the reverse occurs in the arsenic eaters of Styria. These people take a somewhat large dose at once, but they take it in a dry form so it shall not be absorbed too quickly and the eliminating organs pass it out of the body with sufficient rapidity to prevent poisoning. It is highly probable that a small quantity may circulate in the blood for a long time before the last traces of it are eliminated. Styrian arsenic eaters take their doses at comparatively long intervals, generally a week or a fortnight, but very minute doses regularly taken are said to have the effect of producing plumpness and strength, and in some girls' boarding schools in Switzerland arsenic is said to be regularly put in the food for the purpose of improving the girls' appearance.

Tolerance is a condition which it is difficult or impossible to explain fully, and there are probably various kinds of it. In cases of pneumonia, tartar emetic used to be given in 20-grain doses without causing any vomiting. This want of emetic action may have been due to some extent to the absence of hydrochloric acid in the stomach during the febrile condition, and where tartar emetic has been given several times, rejected at first but retained afterwards, its retention may have been due to the absence of hydrochloric acid due to gastric catarrh produced by the first few doses. It is quite probable, however, that its tolerance in pneumonia may have been due partly to the altered tissue change in this disease, which is evidenced by the absence of chlorides from the urine.

There can be little doubt that different cells of the organism have different selective powers towards drugs. This is well shown by the different reaction of different cells towards the stains employed in microscopic observation, and is evidenced in the living body by the manner in which the bones become stained in animals fed with madder. If we consider what the condition of a cell will be when a new substance is brought to it by the blood, we may form a hypothesis regarding tolerance which, even if imperfect, may help us to understand the nature of the phenomenon.

New substances will come first of all in contact with the outer part of the cell, so that the relationship of the exterior to

the interior will become altered. Gradually the new substance will penetrate into and pervade the cell uniformly, and unless fresh quantities of the new substance be carried to the blood, the cell may go on almost unchanged in its functional activity. Even if new quantities are supplied to the exterior of the cell, a larger proportion of the new substance than at first will be required to produce the same relative change between it and the interior of the cell, and so it will gradually lose its primary effect, larger and larger doses being constantly required, until at last they seem to have almost no action.

This hypothesis will help us to understand the gradual loss of effect both of purgatives and narcotics, but we must remember that complete imbibition of a cell with a new substance may alter its whole activity, although the relationships of the different parts of the cell to one another are undisturbed. In this way arsenic may tend to cause fatty degeneration and atrophy of various cells, both muscular and nervous, and to produce a series of changes which, though very slow, may surely lead to a fatal result.

In the case of arsenic, the cumulative action which was so well observed in the Manchester epidemic was due to the constant ingestion of a larger quantity than the eliminating organs could remove. The same is the case with mercury and lead, and the sudden appearance of mercurial or lead poisoning is only caused by the accumulated amount becoming at length sufficient to produce symptoms. In the same way the curious greenish-purple of the skin produced by the long-continued use of nitrate of silver occurs after long accumulation, and in the case of this metal it is stated that this undesirable result may follow the use of a small amount of silver if it has been freely administered years before, little or no elimination having occurred in the interval. In the case of two drugs especially—digitalis and strychnine—sudden development of poisonous symptoms has been specially noted. In some cases it is possible that this may have been due to accumulation of the active principle in the intestinal canal, with sudden solution and absorption in consequence of some article of food or drink having been taken, in the same way as I have described with

regard to quinine. But generally I believe it is due to these drugs causing a lessened flow of urine, and thus arresting their own excretion.

Arsenic has long been known to be a most useful drug in malaria, and quinine, its chief rival in this disease, tends in large doses to produce eruptions of the skin and weakness of the circulation. It has, in addition, the power of producing most disagreeable buzzing in the ears and deafness.

Quinine belongs to the so-called aromatic series, and it was the attempt to make quinine artificially which led to the thorough investigation of this series, which has resulted in a number of antipyretics having been prepared synthetically.

Carbolic acid or phenol is one of the simplest members of this series, but nearly every member of it has a tendency, more or less, to produce cutaneous eruptions with feebleness of the circulation, with sometimes a tendency to collapse, and with a tendency also to produce anæmia when administered for a long time. The eruptions vary in character according to their intensity, but most frequently consist either of simple redness, sometimes accompanied by papules, or of a rash resembling urticaria, and accompanied like it by troublesome itching. Carbolic acid, salicylic acid, salicylates, benzoic acid and benzoates, thallin, antifebrin, phenacetin, lactophenone, salol, naphthol, analgine and exalgine have all been noted as producing redness; and although the further stages of papules, vesicles, or urticaria may not have been observed in each of these remedies, it is probably only a question of dose, and any one of them may cause it.

In the case of antipyrin, which is the most frequently employed of all the antipyretics, not only have scarlatiniform rashes, urticaria, miliary vesicles, and much cutaneous irritation been observed, but even hæmorrhagic rashes have been noticed. Turpentine, and substances allied to it in chemical composition, such as copaiba, cubebs, and essential oils, have a similar tendency to produce erythematous and vesicular rashes with intense itching, and borax and boric acid produce mottled redness, while sulphonal may give rise to a red rash, and chloral to one which is both red and papular. The effect

of bromides and iodides is so well known that I need not do more than allude to it here. I should, however, mention the effect that the local application of calomel may have upon the eyes of a patient who is taking iodides. The iodide is excreted by the lachrymal gland, and appears to give rise to the formation of mercuric iodide, which, being a powerful irritant, causes severe inflammation of the eyes if calomel be locally applied to them at the same time. The drugs which I have already mentioned as acting on the skin and producing rashes probably do so by a local action during the process of elimination, in the same way as arsenic, although this may be aided to a certain extent by a general action on the nervous system in the case of salicylic acid and several of its congeners, which often cause much sweating. There are several drugs which produce red rashes which are accompanied, not by sweating, but by extreme dryness of the skin. These are belladonna, atropine, stramonium, hyoscine, and solanine, all substances obtained from the natural order *Solanaceæ* or its subdivision, *Atropaceæ*. The redness which they produce is generally diffuse, and more usually resembles the rash of scarlatina than that of measles or urticaria.

Antidiphtherial serum very frequently produces rashes which may resemble scarlatina, measles, or urticaria, and in one case where I used antistreptococcus serum for ulcerative endocarditis, the effect was both astonishing and alarming. The whole subcutaneous tissue of the body became œdematous, and the eyelids so swollen as to almost close the eyes, so that the patient presented the typical appearance of a man suffering from extremely bad chronic nephritis.

Morphine does not often cause a rash, but it sometimes causes very troublesome itching, and it may have a very marked effect upon the vessels of the skin, leading to flushing. Such flushing is still more marked in persons who are accustomed to taking chloral; it may not be evident in ordinary circumstances, but it becomes very annoying if the patient takes any alcohol, and sometimes even after food.

Nearly all the substances that I have mentioned as acting on the skin tend also to enfeeble the circulation and give rise,

if long continued, to a feeling of weakness, or even to sudden fainting. In the case of a patient of mine who was accustomed to take morphine, fainting and loss of consciousness occurred when the patient quickly rose to a standing position. This would appear to indicate that the fainting is rather due to vascular dilatation than to cardiac weakness. In the case of cardiac tonics, such as digitalis and strophanthus, the excessive slowness of the heart which may occur when the drug is pushed to too great an extent may lead to sudden syncope of a fatal character, and this is all the more likely to happen if the patient is not only in the upright position, but is attempting to micturate. The cardiac tonics appear to be eliminated by the mucous membrane of the stomach, and in this process give rise to irritation, with nausea and sickness. This may pass off by merely stopping the administration of the drug, but their disappearance may be accelerated by giving large draughts of water so as to wash out the contents of the stomach completely, while any of the water absorbed will tend to hasten their elimination by the kidneys.

Another drug that is said to have a very depressing action upon the heart is chloral, and no doubt it has this action to a considerable extent; but my friend, Professor Liebreich, has pointed out that when chloral is taken continuously it tends to lessen the alkalinity of the blood by yielding formic acid in its decomposition in the body. For this reason he strongly advises that alkalies such as sodium or potassium bicarbonate should always be taken when chloral is used regularly, a piece of advice which I think is not often heeded.

Nearly all the drugs belonging to the benzine series have not only an antiseptic and an antipyretic, but also an anti-neuralgic action, and salicylate of soda, phenacetin, exalgine, and still more antipyrin are all used for the relief of headache and other forms of pain. In cases of neuralgia I believe that a greater or less degree of alkalinity of the blood may influence the pain, but this subject would occupy too much time, and I have written a small paper on it for communication to this Section. For some time past I have used a method of treatment in appendicitis which has given very satisfactory results.

It consists in administering sodium salicylate and belladonna in very full doses. I usually prescribe 15 or 20 grains of salicylate every two hours and 10 or 15 minims of the new tincture of belladonna. The drugs may either be given at the same time or in alternate hours, but they are not mixed because each drug should be taken until the first symptoms of its physiological action appear, singing in the ears in the case of salicylate, and dryness of the mouth, dilatation of the pupil, or quickness of the pulse in the case of belladonna. When these symptoms appear the drug is either to be stopped entirely or greatly diminished in quantity. In two cases the patient has become delirious before any dryness of the mouth or any other symptom of physiological action of the belladonna appeared, but in both cases I found that a tendency to insanity was present in the family. Both patients had been perfectly sane all their lives, but the belladonna appeared to develop the latent tendency for the time being. It is difficult or impossible to explain this curious effect of belladonna upon the brain, and it is also very difficult to explain why antineuralgics sometimes intensify instead of relieving pain, or why narcotics sometimes fail to act and at other times produce excitement instead of sleep.

When I was working in Professor Ludwig's laboratory, it was the custom always to narcotize a dog before an experiment by injecting a quantity of laudanum directly into the subcutaneous vein which runs across the hock joint of the hind leg. Usually the animal fell into profound coma, from which nothing could arouse it. On one occasion I injected about a drachm of tincture of opium, but, instead of the expected sleep, excitement was produced so that the animal howled and struggled. I immediately injected another drachm with no better result. I again injected a third, and still the excitement continued. Not knowing what else to do I then injected a strong solution of chloral. At once the excitement subsided and the expected coma came on. This showed me that occasionally a mixture of hypnotics may produce much better results than a single one.

Excitement of the circulation tends to counteract the effect of a narcotic upon the brain, as is well known in cases of opium

poisoning where the circulation is kept active by keeping the patient walking and by applying painful stimuli such as a strong faradic current in order to prevent coma. Sometimes the sleeplessness is induced and the effect of the narcotic counteracted by irritation in the stomach due to excessive acidity of its contents and a teaspoonsful of bicarbonate of soda in water by neutralizing the acidity will allow sleep to come on. Another cause of excited circulation is fever, and in febrile cases where sleeplessness is a marked symptom the ordinary narcotics may fail to induce sleep, but if the patient's temperature be reduced by sponging, by packing, or by the administration of some antipyretic such as phenacetin, the narcotics will then take effect or sleep may occur without the use of any narcotic whatever.

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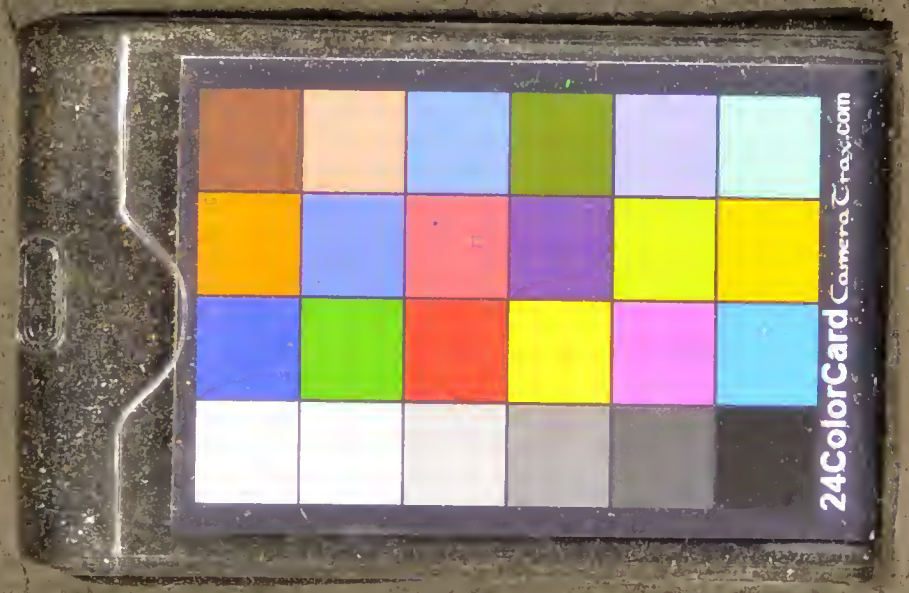
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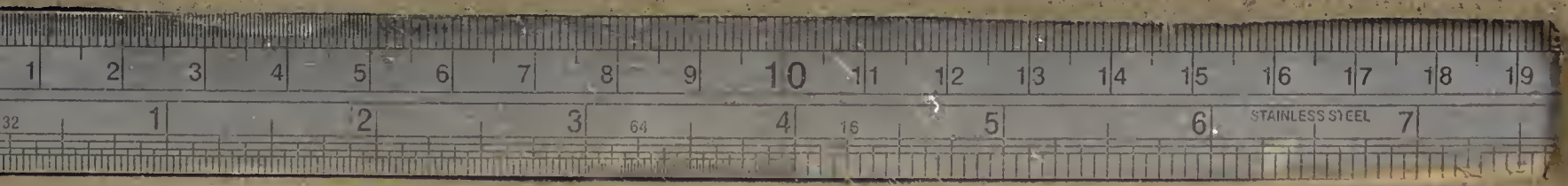
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